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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,675	02/12/2001	Nicholas C. Nicolaides	01107.00098	8276

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EXAMINER

LOEB, BRONWEN

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/780,675

Applicant(s)

NICOLAIDES ET AL.

Examiner

Bronwen M. Loeb

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 October 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-71 is/are pending in the application.
- 4a) Of the above claim(s) 32-70 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-14, 16, 18-25 and 28-31 is/are rejected.
- 7) ☒ Claim(s) 7, 15, 17, 26 and 27 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment filed 16 October 2002 in which claims 1-5, 12-18, 26, 31 and 71 were amended.

It is noted the the amendment filed 16 October 2002 under the section entitled "Claim objections" states "The claims in the case are claims 19-36. Applicants acknowledge, with appreciation, the withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph." Since the claims pending in this case are actually 1-71 and the instant action is the first to respond to Applicant's amendment and arguments (therefore no rejection could have been withdrawn yet), it is believed these sentences are erroneously included in the response. Clarification regarding these statements is required in response to this action.

Claims 1-71 are pending.

Election/Restrictions

1. Claims 32-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Sequence Compliance

2. The amendments to the specification to include sequence identifiers for each sequence disclosed has placed the case in compliance with the sequence rules, 37 CFR 1.821-1.825.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlink is on p. 12, line 6 of the specification.

Response to Amendment

4. The rejection of claims 1-16, 18-25 and 28-31 under 35 U.S.C. §112, first paragraph, scope of enablement, has been withdrawn in view of Applicant's amendment.

The rejection of claims 7 and 15 under 35 USC §112, first paragraph, written description, has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 4 and 13 under 35 U.S.C. §102(b) as being anticipated by Aronshtam et al (Nucleic Acids Research (1996) 24:2498-2504; cited in the Information Disclosure Statement filed 26 April 2002, Paper #11)) has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 3, 18 and 23 under 35 U.S.C. 103(a) as being unpatentable over Wu et al (Journal of Bacteriology (1994) 176:5393-5400) in view of

Winnacker ("From Genes to Clones, Introduction to Gene Technology", Translation by Horst Ibelgaufts, Weinheim, New York, VCH, 1987, pp. 241-242) has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 6, 7, 14, 15, 17, 18, 20, 24-27 and 71 under 35 U.S.C. §103(a) as being obvious over Nicolaides et al (USP 6,146,894), in view of Winnacker and Aronshtam et al, has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 6, 7, 14, 15, 17, 18, 20, 24-27 and 71 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,146,894 in view of Winnacker and Aronshtam et al has been withdrawn in view of Applicant's amendment.

5. Claims 1-6, 8-14, 16, 18-25 and 28-31 stand rejected under 35 U.S.C. §112, first paragraph, as lacking written description for reasons of record and as further discussed below.

Claims 18, 19 and 25 stand rejected under 35 U.S.C. §102(b) as being anticipated by Aronshtam et al (Nucleic Acids Research (1996) 24:2498-2504) for reasons of record and as further discussed below. It is noted that claim 25 was inadvertently listed as claim 29 in the previous action; this was an obvious typographical error as claim 29 is drawn to a mammalian MutL protein while Aronshtam et al clearly teach a prokaryotic mismatch repair gene as recited in claim 25. The Examiner apologizes for this typographical error and any confusion it caused.

6. New grounds of rejection, necessitated by Applicant's amendment, are set forth below.

Response to Arguments

7. With regard to the rejection of claims 1-6, 8-14, 16, 18-25 and 28-31 under 35 U.S.C. §112, first paragraph, as lacking written description, Applicant's arguments have been fully considered but are deemed not persuasive.

Applicant argues that "the claims, as amended, are descriptive of a representative number of species encompassed by the amended claims" (p. 11) and that the specification provides guidance regarding 1) the definition of the dominant negative effect, 2) methods for identifying dominant negative alleles and 3) assays for the dominant negative effect. These arguments are not persuasive. The claims have been amended to recite "a form of a mismatch repair gene ...wherein said form...exerts a dominant negative effect on mismatch repair". This amendment now encompasses expression of wild-type heterologous mismatch repair genes in bacteria, as well as dominant negative alleles of mismatch repair genes. Thus, the claims as amended are now broader in scope than the as-filed claims and therefore the genus encompasses more species. Given that the specification does not teach a representative number of species for the the narrower scope claims, increasing the scope of the claims does not serve to overcome the rejection. Regarding overexpression of foreign mismatch repair genes in bacteria to yield a dominant negative mutator phenotype, the specification cites references 35-37 (p. 18, lines 1-4); none of the three cited articles however discloses expressing human or yeast MMR genes in bacteria. Other prior art teaches that expression of *Streptococcus pneumoniae*

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hexA, a homolog of MutS, in *E. coli* causes hypermutability however expression of hexB, a homolog of MutL, does not (see Prudhomme et al (J. Bacteriology (1991) 173:7196-7203; cited in IDS, Paper #11). Expression of a human homolog of MutS, MSH2, in *E. coli* also causes hypermutability (see Fishel et al (Cell (1993) 75:1027-1038; cited in IDS, Paper #11). The specification teaches that expression of a human homolog to MutL, hPMSR3, in *E. coli* causes hypermutability (Example 2). While these data may suggest that expression of foreign MutS-homologs can cause hypermutability in *E. coli*, one cannot predict the same will be true for MutL homologs. The specification remains deficient in describing a structure-function relationship for Mut H, Mut Y, MLH1, MLH3, MSH2, PMSR or PMSL correlating structure to a dominant negative allele function in bacteria. Since the function of the PMSR genes is not definitively known (see p. 205, final paragraph of Nicolaides et al (1995) Genomics 30:195-206; cited in IDS) the result for hPMSR3 cannot be extrapolated to the other genes in the PMSR family. There is no disclosure of what truncation might in any PMS2 gene from any species other than human would give a dominant negative allele or a dominant negative effect when expressed in bacteria. The fact that the specification teaches methods for identifying dominant negative alleles and assays for dominant negative effect, while germane to an enablement rejection, is not germane to a written description rejection and is thus not persuasive. The rejection is maintained.

8. With regard to the rejection of claims 18, 19 and 25 under 35 U.S.C. §102(b) as being anticipated by Aronshtam et al (Nucleic Acids Research (1996) 24:2498-2504), Applicant's arguments have been fully considered but are deemed not persuasive.

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Applicant argues that Aronshtam et al do not induce the inducible promoter to express the dominant negative alleles. While this argument is persuasive with regard to claims 1,4 and 13, it is not persuasive with regard to claims 18, 19 and 25 because these claims do not contain the limitation that the dominant negative allele be induced, only that when expressed, there is a dominant negative effect when expressed. As Aronshtam et al demonstrated, these mutants cause a dominant negative effect. Thus, the composition claims remain anticipated.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2-5, 12, 13, 16 and 71 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 are vague and indefinite because each was amended to delete the phrase "from any species" or "homolog from any species", which would indicate that scope of each is drawn only to the E. coli gene recited. However, the amendment was accompanied by the statement "The amendment is not intended to change the scope of the claims as filed" (p. 10 of paper amendment filed 16 October 2002). Thus, it is unclear whether each claim is drawn to only the E. coli gene recited or to any homolog

of each gene recited. Therefore the metes and bounds of each of these claims is unclear.

Claim 71 recites the limitation "the dominant negative allele" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 2-5 have been examined assuming that the mismatch repair gene is the recited gene from *E. coli* or any known homology thereof. This is the broadest reasonable interpretation given the lack of clarity in these claims (see rejection above under 35 USC §112, second paragraph).

13. Claims 1, 3, 18, 23 and 25 are rejected under 35 U.S.C. §102(b) as being anticipated by Prudhomme et al (*J. Bacteriology* (1991) 173:7196-7203; cited in IDS, Paper #11). Prudhomme et al teaches expressing the *Streptococcus pneumoniae* gene, *hexA*, in *E. coli* under the control of an inducible hybrid promoter, *mucp*, which requires both maltose and one of lactose and IPTG to express the gene. The resulting transformed cells were hypermutable. *hexA* encodes a mismatch repair protein which is a homolog of *E. coli* MutS. *Streptococcus pneumoniae* is a gram-negative bacteria and

is thus prokaryotic. See entire document, especially the Abstract, p. 7197 "Plasmid Constructions", pp. 7199-7200 "hexA gene expression confers a mutator phenotype on wild-type E. coli" and Table 2.

14. Claim 1, 3, 10, 18, 23, 24, 28 and 31 are rejected under 35 U.S.C. §102(b) as being anticipated by Fishel et al (Cell (1993) 75:1027-1038; cited in IDS, Paper #11). Fishel et al teaches expressing the human gene, MSH2, in E. coli under inducible control of the lac promoter which requires IPTG for induction. The resulting transformed cells were hypermutable as measured by the rate of spontaneous mutation to rifampicin resistance. MSH2 is a homolog of E. coli MutS. Humans are mammals and are eukaryotes. See entire document, especially the Abstract, pp.1029-1039 "Expression of hMSH2 causes a Dominant Mutator Phenotype in E. coli", Figure 4 and pp. 1036-1037 "Mutator Assay".

Conclusion

Claims 1-6, 8-14, 16, 18-25, 28-31 and 71 are rejected. Claims 7, 15, 17, 26 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 11:00 AM to 7:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

December 29, 2002



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